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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 00D-0186; *Draft Guidance on M4 Common Technical Document*

Dear Sir or Madam:

Thank you for this opportunity to review the *draft* guidance on the *M4 Common Technical Document*. Pharmacia appreciates the progress that has been made on this very important initiative.

Our comments are attached. Should any clarification of our input be required, please don't hesitate to contact me at (616)-833-8141.

Sincerely,

Pharmacia Corporation

Jenny L. Peters
Director
Regulatory Intelligence
Global Regulatory Affairs

00D-0186

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THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE - SAFETY

General Comments

- The guidelines have been clarified regarding many major points and we agree with the overall structure and content.

- We also agree with the present general instructions for the "Nonclinical Overall Summary" and the "Nonclinical Written Summaries." The document guides the author in preparing consistent and logical documentation. The clarification regarding handling and placement of toxicokinetic data is welcomed.

Specific Comments - "Nonclinical Overall Summary" and "Nonclinical Written Summaries"

- "General Aspects" on page 3 and "Use of Tables and Figures" on page 7: The desired method of referencing within the text of the documents appears clearer than previous versions. Specifically, the guideline indicates that reference citations to the Tabulated Summaries and Study Report Number should be included throughout the text of the written summaries. The list of references is for literature citations only. We interpret this to mean that the Technical/Study Reports will be located only through the Tabulated Summaries (location: volume and page). If this is not correct, please edit the guideline with more information.

- Section 2.1: "Order of Presentation of Information within Sections" does not include humans. Presentation and discussion of the human radiolabeled absorption/excretion study is routinely included in the nonclinical section of our submissions. If this should be an element common to all submissions, please add it after "9. Non-mammals."

- Section 3.3.3, "Absorption": If this section should routinely include discussion of repeated dose studies and toxicokinetic parameters beyond that needed for the Drug Safety studies, please indicate this under the "Kinetic parameters." We noted that the Tabulated Summaries section already provides for repeated dose studies.

Specific Comments – "Nonclinical Tabulated Summaries"

- The addition of a page of definitions would be helpful to avoid confusion about the meanings of some of the table headings and parameters (e.g., it will be particularly important to establish a common definition of "notable findings").

- We assume that non-pivotal studies in any area will not have to be listed in separate tables. There is a template given for a single table listing all non-pivotal repeated-dose toxicity studies and, similarly, a single table for non-pivotal reproduction toxicity studies. However, non-pivotal studies are often performed in the other areas (single-dose toxicity, genotoxicity, safety pharmacology, etc.). We presume that these will appropriately be

listed in a similar manner. One possible suggestion is to list all non-pivotal studies on one single template with subheadings for the different areas.

- Regarding the genotoxicity tables:

  1) to be consistent with the other toxicology tables, we recommend that genetox assay results only be listed in cases where the findings are considered "notable," i.e., where positive evidence of genotoxicity exists, and
  2) we would like to see an example of a tabulated summary for a mammalian cell mutation assay.

- There are a number of typographical errors in the templates and examples that we presume will be corrected as the instructions are finalized. We would be happy to provide a list of specific typos upon request.

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE - EFFICACY

General Comments

- Module II is to contain the CTD Summaries, including the "Written Summary of Human Studies and Experience." We would usually write the clinical data documentation to support the product labeling, which would mean that Module II should be written to support the information that is contained in Module I, i.e., the labeling.

  Since each country may have different requirements for labeling, we wonder if it is logistically possible to write the documentation in Module II in such a way that it supports the region-specific requirements for labeling (as will be contained in the various Module Is)? For example, sponsors usually have a pre-NDA meeting, where the sponsor and US FDA reach an agreement regarding the types of safety and efficacy displays, the pool of studies which will be used to derive the adverse event data for the labeling, and the issues to explore in more depth. Thus, in light of this regional specificity, it would appear necessary to produce several versions of Module II. This approach would negate the full benefit of the CTD.

  If, on the other hand, Module II is to be written to support so called "core labeling," perhaps this could be clarified in the guidance.

- It should be noted that the "Written Summary of Human Studies and Experience" is referred to in multiple ways within the guidance documents, e.g.,

  ⇒ "Clinical Written Summary" (reference the "Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use"; in the pyramid and in the table of contents of the document)

⇒ "Written Summary of Human Studies and Experience" (reference the "Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use"; in the 5th paragraph on page 2)

⇒ "Written Summary of Clinical Studies and Experience" (reference "The Common Technical Document for the Registration of Pharmaceuticals for Human Use – Efficacy")

For clarity reasons, the same terminology should be used consistently throughout the guidelines to refer to a given document.

- The title of this document, i.e., "Efficacy," could be misleading, since it really describes both efficacy and safety information, as provided in the "Clinical Overall Summary" (COS) and the "Written Summary of Clinical Studies and Experience."

Specific Comments – "Clinical Overall Summary" – Module II

- The COS appears to be analogous to the Clinical Expert Report. However, unless one has prepared a Clinical Expert Report before, it would be difficult to understand how the data should be presented in this document. For example, on page 3, the guidance states, "The following issues should generally be discussed...." However, it is unclear what type of data presentations should be used to discuss them, e.g., it is unclear whether a by-study presentation of data, a side-by-side display of data across studies, or just narrative text addressing each of the issues, with references to the supportive documentation, is needed. Ideally, these guidelines would have a level of detail that is more similar to that stipulated for study reports in the ICH Guidelines for Clinical Study Reports. This would ensure that sponsors are providing the necessary information in an acceptable format.

- It is suggested that a Table of Contents (TOC) for the COS be added. This would be useful and consistent with providing a TOC for the "Written Summary of Clinical Studies and Experience" section.

- In Section 9, "References" (page 6), the guidance states, "A list of references used, in addition to those contained in the dossier, should be given...."; are these the key references which are to be included in Module V? If yes, perhaps this can be directly stated in the guidance.

Specific Comments – "Written Summary of Clinical Studies and Experience" – Module II

- In contrast to the COS, no introductory information is provided to orient the user as to the purpose of the "Written Summary of Clinical Studies and Experience." This document appears to be similar to the current optional Written Summary of an EU Dossier (usually <100 pages); however, no page restriction is given. We believe the addition of descriptive introductory information would be useful.

- Section 1.1; "Background and Overview": Contents of this section include "an overview of analytical methods used." It should be specified whether this refers to only bioanalysis (measurement of drug in bodily fluids, such as plasma, serum, etc.) or also analytical methods for measurement of drug release (the in vitro dissolution profile database). Inclusion of both is implied in the "Guideline on Organization of Clinical Study Reports and Related Information in Module V (Clinical) of The Common Technical Document (CTD)," Section 1.4.

- Section 1.2; "Summary of Results of Individual Studies": A reference to individual study synopses for the biopharmaceutic and analytical methods is missing. In Section 2.2, it is stated that "The ICH E3 synopses of the individual studies should be included collectively in section 5 of this written summary document."

- Sections 1.2, 2.2 and 3.2 require essentially the same information as Section 5 ("Synopses of Individual Studies;" ICH E3 synopsis). It may be better to have in Section 5 the ICH E3 guideline table entitled "Listing of Clinical Studies" described in the guideline for Module V, with a column to include cross-referencing to subsections 1.2, 2.2 and 3.2, where the synopses of each study would be placed. Alternatively, all synopses could be placed in section 5 and the sponsor could indicate by cross-reference where to find the synopsis of each of the pertinent studies in subsections 1.2, 2.2 and 3.2. These alternative methods would cut down on the repetition in the same document.

- Section 1 "Appendix" (page 3): The recommended tabular content for reporting results of bioequivalence studies ("mean ratios (test/reference) for Cmax and AUC and their 90% confidence interval") are based on current metrics. To accommodate possible future changes in statistical tests for assessment of bioequivalence, more generic wording may be appropriate here. Alternatively, "...or the currently recommended metrics for bioequivalence assessments" could be added to the current statement.

- The example table for efficacy (Table 3.1) does not include duration of therapy. Table 3.2 would presumably summarize efficacy data by study; however, it is interesting that such a table is not proposed for use in the COS. We feel one would be useful.

- The examples of the safety tables could cause confusion: Tables 4.1 and 4.2 show examples pertinent to integrated databases, while Tables 4.3 and 4.4 show examples pertinent to individual study presentations (although Table 4.3 includes a "total" column, following the individual study displays). The ultimate goal is to support the product labeling; however, as noted previously, this does not seem to be emphasized enough when the guidelines talk about data presentation. It would be highly unlikely that one would present adverse event data on a study-by-study basis (except perhaps for clinical pharmacology trials); yet, this option is presented without any discussion of the potential risks associated with it. Obviously, it might be easier to provide by-study summaries rather than to integrate data; however, the purpose of integrating safety data is to more fully characterize the adverse event profile of the drug.

- Since the European Tabular Formats have been in use for some time, we wonder why CTD does not take advantage of these documents. Without direction, companies will make up their own internal templates as the guidance states that these tables are not to be considered templates. Agencies will see many variations on a theme and are less likely to get what they need.

ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Specific Comments – Module V

- Module V is to contain the Clinical Study Reports and related information. In the Table of Contents of the CTD, the content of this module is specified as:

  A. Table of Contents
  B. Study Reports
  C. Key Literature References

  However, when one reviews the "Efficacy" document, one finds that reports of any pooled analyses of data across studies, e.g., an extensive safety summary or subpopulation analysis, should also be included in this section. The inclusion of such reports is not clearly stipulated in the Table of Contents of Module V.

- It is not clear what is meant by "key" literature references (e.g., only the cited articles that are needed to support a specific argument, articles that might present epidemiologic data to put the disease into perspective but that are not needed to interpret the data). Is the idea that literature cited be limited to a few relevant articles as some journals do? In the past, our firm has generally included copies of all cited published papers both in NDAs and in Clinical Expert Reports. We note that the ICH Guidelines for Study Reports require that copies of "important" referenced publications are included in an appendix. We ask that the desired level of references be clarified.